FINAL REPORT

George H. Scherr June 30, 1954

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The Creighton University, School of Medicine
Omaha, Nebraska

Title of Project: The Therapy of Systemic Moniliasis in Mice

Observations that pregnant mice showed a higher degree of resistance to infection with Candida albicans than non-pregnant females or males (Scherr and Weaver, 1951) prompted an investigation of the effects of various gonadotropic hormones on male and female mice infected with moniliasis. By controlling and altering the types of gonadotropins used, route of injection of hormones, severity of infection, dosage amount, and schedule of treatment, it was found that it was possible to significantly decrease the severity of the infection upon treatment with certain gonadotropins, under rather exacting conditions. Tables 1 to 5 inclusive summarize these results for the various gonadotropic hormones used, including whole pregnant mouse serum; the mean dissemination values are computed as previously described (Scherr, 1953c).

On the basis of observations such as that of Sohval and Soffer (1951) indicating that treatment with cortisone may increase the titer of urinary gonadotropins, studies were undertaken to ascertain the effect of cortisone and/or somatotrophic hormones (STH) on Candida-infected mice.

It was found that under certain conditions cortisone would significantly reduce the mortality rate of infected animals but to varying degrees depending among other factors, upon the sex of the animal. These results and other pertinent data are presented in greater detail in other papers (Scherr, 1953a, 1953b, 1953c, 1953d 1953f). They are in accord with findings of other

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investigators working with other infectious agents (Duffy and Morgan,1951; Kilbourne, 1952; Robinson et.al.,1953).

The physiological antagonism between STH and cortisone was corroborated under the conditions of these studies and in a manner which supported our thesis that cortisone may be deleterious or efficacious to certain infectious states depending upon the conditions and environment of the infected host. It should be possible, by a suitable control of these conditions, to preferentially antagonize the deleterious properties of cortisone without suppressing its efficacious effect. The practical possibility of this approach to the therapy of certain infectious states gained some support from studies using mice infected with moniliasis (Scherr,1953d,1953e) and embryonated eggs infected with vaccinia virus (Severens et.al.,1954; Scherr et. al., 1954).

Because the sex of the animal plays a major role in the response of infected and uninfected mice to treatment with cortisone and/or STH (Scherr, 1952,1953d), studies were undertaken to ascertain the influence of sex hormones, either alone or in combination with cortisone and STH, on this infectious state. These data are summarized in the tables 6,7, and 8 and have been presented in greater detail in other papers (Scherr,1954a).

One of the most significant features of these results is that testosterone enhanced the deleterious effect of cortisone on infected male and female mice and that this synergistic deleterious effect increased with an increased dosage of testosterone. In addition, a mixture of cortisone and testosterone, at dosage levels which had no toxic effect on normal mice when used alone, resulted in a mortality of 40% when inoculated into normal male animals. This toxic effect of the mixture was suppressed to a very slight degree by the dosage of STH used here.

The study reported here is in accord with the precept that there is an interplay of adrenal-cortical and other hormones which tends to maintain a state of resistance or susceptibility to infectious diseases. This activity is essentially non-specific and affects the resistance of the host through the effect on numerous bodily functions, e.g., capillary fragility, inflammatory response, antibody formation, salt and fluid balance, and many others. If alteration in the performance of these bodily functions by induced changes in the concentrations of various hormones enhances the susceptibility of the host to infection with certain pathogenic agents, then it should be feasible to supress active infectious states by exerting an influence on the above-mentioned bodily functions by judicious injections of proper kinds and concentrations of certain hormones and other agents. It has thus been possible to show that a particular dose schedule of cortisone STH, and hesperedin methyl chalcone almost completely obliterated any signs of experimental moniliasis in female mice but not in males, and that this same treatment schedule was ineffective for both sexes when the severity of the infection was altered (Scherr, 1954b).

Table 1

Effect of Normal Pregnant Mouse Serum on Mice Infected with Moniliasis

(Duration of experiment - 15 days)

Legend	Sex	No. Mice	Mean dissemination value	Averaged mean value
Infected, untreated	M	5	4.2	
	F	4	4.0	4.1
Infected, treated daily with 0.2 ml of pregnant mouse serum	M	5	1.0	
	F	5	2.2	1.6

t 4.44
Deg. of freedom 17
P . . . . . < .005

Table 2

Effect of Gonadotropin from Pregnant Mare's Serum (Gonadogen)

on Mice Infected with Moniliasis

(Duration of experiment = 23 days)

Infected mice treated with Gonadogen	No. Mice	Sex	Mean dissemination value	Mortality (%)
Untreated (4-73A)	30	M	1.0	0.0
0.4 I.U. (0.1 ml) per mouse per day, subcut., treatment started day after infection (4-73E)	30	M	2.1	10.0
Treated as in 4-73E but started 15 days after infection (4-74A)	26	M	5.0	34.6
Treated as in 4-73E but dose doubled every 6 days (4-74I)	30	M	4.3	23.4
Untreated (4-73B)	30	F	1.4	3.3
Treated as in 4-73E (4-73F)	30	F	1.4	3.3
Treated as in 4-74A (4-74B)	26	F	4.3	26.9
Treated as in 4-74I (4-74J)	30	F	1.3	3.3
Infected with mucin adjuvant, untreated (4-73C)	30	M	8.7	50.0
Infected as in 4-73C, treated as in 4-73E (4-73G)	28	M	8.8	46.4
Infected as in 4-73C, treated as in 4-74A (4-74C)	59	M	8.9	50.9
Infected as in 4-73C, untreated (4-73D)	30	F	8.6	46.7
Infected as in 4-73C, treated as in 4-73E (4-73H)	20	F	8.4	46.7
Infected as in 4-73C, treated as in 4-74A (4-74D)	59	F	7.0	45.8

Table 3

Effect of Gonadotropin from Pregnant Mare's Serum(Gonadogen)

on Mice Infected with Moniliasis

(Duration of experiment = 23 days)

Infected mice treated with Gonadogen	No. mice	Sex	Mean dissemination value	Mortality (%)
1.6 I. U. (0.1 ml) per mouse per day, subcut., treatment started day after infection (4-82E)	60	M	6.5	35.0
Treated as in 4-82E but treatment started 15 days after infection (4-82M)	58	M	4.1	29.3
Treated as in 4-82E but dose doubled every 6 days (4-83H)	30	M	11.3	60.0
Untreated (4-82B)	30	F	3.2	20.0
Treated as in 4-82E (4-82F)	60	F	6.4	33.3
Treated as in 4-82E but treatment started 15 days after infection (4-83A)	60	F	4.4	23.4
Treated as in 4-82E but dose doubled every 6 days (4-83I)	30	F	9.4	46.7
Infected with mucin adjuvant, untreated (4-82C)	30	M	23.2	100.0
Infected as in 4-82C, treated as in 4-82E (4-82G)	60	M	21.1	93.3
Infected as in 4-82C, treated as in 4-82M (4-83B)	60	M	21.8	95.0
Infected as in 4-82C, treated as in 4-82E but dose doubled every 6 days (4-83J)	29	M	15.0	62.1

Table 3 (cont'd)

Infected mice treated with Gonadogen	No. mice	Sex	Mean dissemination value	Mortality (%)
Infected as in 4-82C, untreated (4-82D)	30	F	25.9	100.0
Infected as in 4-82C, treated as in 4-82E (4-82H)	60	F	22.2	91.8
Infected as in 4-82C, treated as in 4-82M (4-83C)	60	F	24.7	90.0
Infected as in 4-82C, treated as in 4-82E but dose doubled every 6 days (4-83K)	30	F	9.1	53.3
Infected as in 4-82C, treated with 2d4 I. U. (0.1 ml) Gonadogen per mouse per day, subcut., dose doubled every 6 days (4-83L)	30	M	15.6	66.7
Infected as in 4-82C, treated as in 4-83L (4-83M)	30	F	14.0	60.0

Table 4

The Effect of Gonadotropin from Human Pregnancy Urine (Pranturon) on Experimental Moniliasis in Mice

(Duration of experiment = 25 days)

Legend [1]	Sex	Mean dissemination value	Mortality (%)
Infected, untreated (4-13B)	M	20.5	70.0
Infected, treated with 0.8 I. U. (0.1 ml) intramuscularly (4-13D)	M	19.8	70.0
Infected, treated with 1.6 I.U. (0.2 ml) intramuscularly (4-13F)	M	23.9	90.0
Uninfected, treated with 1.6 I.U. (0.2 ml) intramuscularly (4-13H)	M	4.0	20.0
Infected, untreated (4-13I)	F	19.5	70.0
Infected, treated as in 4-13D (4-13L)	F	3.3	20.0
Infected, treated as in 4-13F (4-13N)	F	17.0	60.0
Uninfected, treated as in 4-13F (4-13P)	F	0.0	0.0
Infected, treated with 0.8 I.U. (0.1 ml) subcut. (4-14B)	M	20.6	90.0
Infected, treated with 1.6 I.U. (0.2 ml) subcut. (4-14D)	M	20.0	80.0
Infected, treated with 0.8 I.U. (0.1 ml) subcut. (4-14H)	F	22.6	80.0
Infected, treated with 1.6 I.U. (0.2 ml) subcut. (4-14J)	F	24.6	90.0
Uninfected, treated as in 4-14J (4-14E)	M	4.7	20.0
Uninfected, treated as in 4-14J (4-14K)	F	3.3	20.0
Uninfected, inoculated solely with mucin adjuvant (4-13G)	M	2.6	10.0

Table 4 (cont'd)

Legend	Sex	Mean dissemination value	Mortality (%)
Uninfected, inoculated solely with mucin adjuvant (4-130)	F	2.2	10.0
t comparing 4-13I to 4-13L		3.6	
P		0. - .001	

[1] Treatment with Pranturon using the 5 per cent mucin adjuvant, was in all cases instituted 2 days after infection and repeated daily for the duration of the experiment. Ten mice constitute an experimental group in every case.

Table 5

The Effect of Gonadotropin from Pregnant Mare Serum (Anteron) on Experimental Moniliasis in Mice (Duration of experiment - 29 days)

Legend [1]	Sex	Mean dissemination value	Mortality (%)
Infected, untreated (3-230D)	M	10.4	80.0
Infected, treated (3-240F)	M	11.6	30.0
Infected, untreated (3-239D)	F	5.1	10.0
Infected, treated (3-239F)	F	3.1	10.0
Uninfected, treated as above (3-219E)	M	0.0	0.0
Uninfected, treated as above (3-239H)	F	0.0	0.0
Infected with mucin adjuvant, untreated (3-240E)	M	16.0	70.0
Infected as in 3-240E, treated (3-240G)	M	8.1	30.0
Infected as in 3-240E, untreated (3-239E)	F	18.0	60.0
Infected as in 3-240E, treated (3-239G)	F	10.2	50.0
Uninfected, inoculated with mucin adjuvant only (4-239I)	F	0.0	0.0

t comparing groups 3-240E and 3-240G 2.86
P . . . . . .02 .01

[1] Treatment consisted of the intramuscular inoculation of 0.8 I.U. (0.1 ml) of the anteron, which in all cases was instituted 2 days after infection and repeated daily for the duration of the experiment. Ten mice constitute an experimental group.

Table 6

The Effect of Cortisone, Somatotrophic Hormone (STH), and Testosterone on Experimental Moniliasis in Mice

(Duration of Experiment = 29 days)

Infected mice treated with [1]	No. Mice	Sex	Mean Dissemination value	Mortality (%)
Untreated (4-122A)	20	M	6.3	30.0
Testosterone (4-123A)	20	M	7.9	30.0
Testosterone (2x), (4-159E)	19	M	6.5	25.0
Testosterone & cortisone (4-122S)	20	M	15.9	85.0
Testosterone (2x) & cortisone (4-159c)	20	M	18.8	95.0
Cortisone (4-122E)	20	M	12.7	80.0
Testosterone & STH (4-122U)	20	M	6.8	40.0
STH (4-122C)	20	M	11.1	55.0
Cortisone, testosterone, & STH (4-122W)	20	M	10.6	65.0
Cortisone & STH (4-122G)	20	M	14.5	90.0
Untreated (4-122B)	20	F	3.4	10.0
Testosterone (4-123B)	20	F	16.2	85.0
Testosterone (2x), (4-159F)	(no data available)			
Testosterone & cortisone (4-122T)	20	F	11.5	70.0
Testosterone (2x) & cortisone (4-159D)	20	F	15.7	85.0
Cortisone (4-122F)	20	F	11.1	65.0
Testosterone & STH (4-122V)	20	F	7.9	40.0
STH (4-122D)	20	F	7.0	40.0
Cortisone, STH, & testosterone (4-122X)	20	F	10.3	55.0
Cortisone & STH (4-122H)	20	F	10.8	70.0

Table 6 (cont'd)

[1] For details of treatment schedules see text. In order to facilitate the presentation and discussion of these and other data which follow, each group of animals has been assigned a code number.

Table 7

The Effect of Cortisone, Somatotrophic Hormone (STH), and Testosterone on Normal Mice [1]

Uninfected mice treated with	No. mice	Sex	Mean Dissemination value	Mortality (%)
Testosterone 9(4-159W)	20	M	0.0	0.0
Testosterone & Cortisone (4-159Q)	20	M	7.3	40.0
Cortisone (4-123S)	20	M	0.0	0.0
Testosterone & STH (4-159S)	20	M	7.4	30.0
STH (4-158C)	20	M	11.2	50.0
Testosterone, cortisone, & STH (4-159U)	20	M	4.6	35.0
Cortisone & STH (4-158E)	20	M	1.9	10.0
Testosterone (4-159X)	20	F	0.0	0.0
Testosterone & cortisone (4-159R)	20	F	0.3	5.0
Cortisone (4-123T)	20	F	0.0	0.0
Testosterone & STH (4-159T)	20	F	5.6	25.0
STH (4-158D)	20	F	2.3	15.0
Testosterone, cortisone, & STH (4-159V)	20	F	0.5	5.0
Cortisone & STH (4-158F)	20	F	4.1	20.0

[1] These animals were treated simultaneously with and similarly to those described in Table 1.

Table 8

The Effect of Cortisone, Somatotrophic Hormone (STH), and Estradiol on Experimental Moniliasis in Mice

(Duration of experiment = 29 days)

Infected mice treated with [1]	No. mice	Sex	Mean Dissemination valus	Mortality (%)
Estradiol (4-123I)	20	M	15.2	70.0
Estradiol & cortisone (4-123C)	20	M	11.0	70.0
Estradiol & STH (4-123E)	19	M	3.6	10.5
Cortisone, estradiol, & STH (4-123G)	20	M	15.9	75.0
Estradiol (40123J)	20	F	3.1	10.0
Estradiol & cortisone (4-123D)	20	F	17.0	90.0
Estradiol & STH (4-123F)	20	F	20.1	75.0
Cortisone, estradiol, & STH (4-123H)	20	F	19.1	90.0

[1] For details of treatment schedules see text. Control data for infected and normal male and female mice treated with cortisone and/or STH are recorded in Table 1 and 2.

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